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HAMA, JOANNE	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,097	ARENAS ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,14-16,18-24,26-29,31,32,40,46,47,52,54 and 56* is/are pending in the application.

4a) Of the above claim(s) *3,14,22-24,27,46,47,52,54 and 56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,7,15,16,18-21,26,28,29,31,32 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group 1 in the reply filed on August 1, 2007 is acknowledged. The traversal is on the ground(s) that the Examiner's reliance on Lee et al. is misplaced and thus, the claims do not lack the same or corresponding special technical feature. Applicant indicates that the claimed invention is a novel method for inducing or promoting dopaminergic neuronal development in a stem, progenitor, or precursor cell and entails expressing a nuclear receptor of the Nurr1 subfamily above basal levels and then contacting the cells with a Wnt ligand. Claim 52 specifies similar method steps and further comprises isolating a growth factor or factors from such treated cells. Lee et al. are wholly silent as to the recited method steps for inducing or promoting dopaminergic neuronal development. The method described in Lee et al. entail culturing the cells in serum free medium which lacked basic fibroblast growth factor, see Johe et al. (Applicant's response, pages 2-3). In response, this is not persuasive. The Examiner relied upon the teaching of Lee et al. for meeting the limitation of claim 1 that Nurr1 need to be expressed above basal levels within a stem cell and that the cell had to be treated with any Wnt ligand. In Figure 1, Lee et al. show that at stage 3, ES cells that overexpress Nurr1 and Wnt1. Because this teaching meets the limitation of claim 1 Lee et al. would arrive at dopaminergic cells, as claim 1 indicates that those are the limitations used in the method. With regard to the reference of Johe et al., there is no requirement whether or not the media has fibroblast growth

factor in claim 1. As such, because the concept of expressing Nurr1 in ES cells and treating them with Wnt1 was known in the art, the invention lacks unity.

Applicant indicates that guidelines offer certain examples of where unity can clearly be acknowledged to be present and that it would be incorrect to say that unity of invention can only be acknowledged for these examples. The fact that unity must be acknowledged in these situations identified by the Examiner at the top of page 3 of the Office action does not mean that unity will be absent in other situations (Applicant's emphasis, Applicant's response, page 4). In response, Applicant is correct that the guidelines offer examples where unity is found between certain combinations of the product, the method of using the product, and the method of making the product. However, as discussed above, the instant invention lacks unity because Lee et al. teach the method described by claim 1.

Applicant indicates that the PCT Examiner of the instant application did not make a lack of unity finding and considered all of the claims to be directed to a single invention. As such, the instant restriction requirement fails to comply with the established USPTO practice of following the international rules regarding unity of invention in the prosecution of applications filed under 35 USC § 371 (Applicant's response, page 5). In response, actions taken by the Examiner during the international stage of the case are not binding.

Applicant indicates that the invention has unity and that the specification technical feature is the inducement or promotion of dopaminergic neuronal development. This is achieved by 1) expressing a nuclear receptor of the Nurr1

subfamily above basal levels in the cell and 2) treating the cell with a Wnt ligand. This is not taught by the prior art and is explicitly recited in claims 1 and 52 (Applicant's response, pages 5-6). In response, Lee et al., Figure 1 teach ES cells that express Nurr1 and Wnt1 and because Lee et al. teach the limitations of claim 1, the invention lacks unity of invention.

Applicant refers to MPEP §1893.03(d) and indicates that some of the language above is recited in the PCT rules (Applicant's response, page 7). In response, it is not clear what argument Applicant is putting forth. If Applicant is indicating that there is inconsistency between the lack of unity at the international stage and the national stage of the instant application, it is noted that the citation does not indicate that the international stage and national stage lack of unity have to be the same. The first cited paragraph provided by Applicant indicates where unity of invention is applicable, but does not indicate whether an Examiner in the international stage or national stage must necessarily agree if there is lack or unity of not in the application.

Applicant indicates that the Examiner contends that the two groups of invention require different and distinct steps from each other, yet acknowledges the presence of a relationship. If all the claims share a special corresponding technical feature, then they must be considered to be unified and be allowable in one application (Applicant's response, pages 7-8). In response, as discussed above, the inventions do not relate to a single general inventive concept because Lee et al. teach the limitations of claim 1. As such, a lack of unity was carried out.

Applicant indicates on page 4 of the Official Action, the inventions were further restricted. With regard to the election of one family member elected from claims 2 and 3 and if Nurr1 is elected, Applicant must either elect nucleic acid or protein (claims 4 and 5), and further that DNA or RNA must be elected if Applicants elect Nurr1 nucleic acid. Applicant indicates that the restriction is unsound and that it is more appropriate as an election of species. Should Examiner maintain her position, a claim limited to delivery of DNA encoding a nuclear receptor of the Nurr1 subfamily could be readily avoided by a competitor via the delivery of an mRNA encoding the same protein molecule (Applicant's response, page 8). In response, the Examiner has reconsidered the restriction between RNA and DNA of Nurr1 (claim 4) and withdraws the restriction. However, the claims remain restricted between protein and nucleic acid particularly because the method as described in claim 5, requires a protein, which is a different product from that of a nucleic acid. As discussed above, because there is lack of unity, distinct products of Nurr1 nucleic acid and protein are separable.

With regard to the restriction of claim 16, Applicant refers to MPEP 803 and indicates that if the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they may be directed to independent and distinct inventions. Applicant indicates that a requirement for an election of species is more appropriate and consistent with the guidance provided in the MPEP than a restriction requirement (Applicant's response, pages 9-10). In response, according to the

guidelines in Section (f)(i)(a) of Annex B of the PCT Administrative Instructions, the special technical feature as defined by PCT Rule 13.2 shall be considered to be met when all the alternatives of a Markush-group are of similar nature. For chemical alternatives, such as the claimed polynucleotide sequences, the Markush group shall be regarded as being of similar nature when:

(A) all alternatives have a common property or activity and

(B)(1) a common structure is present, i.e., a significant structure is shared by all of the alternatives or

(B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to an art recognized class of compounds in the art to which the invention pertains.

The compounds do not meet the criteria of (A), common property or activity or (B)(2), art recognized class of compounds. While the compounds listed in claim 16 seem to be drawn to substances that similarly activate the retinoid pathway, it is unclear if "a repressor of the retinoid acid receptor (RAR)" is necessarily drawn to that same biological activity as the other compounds listed in claim 16. In addition to this, each of the compounds in claim 16 effect different levels of response of the retinoid pathway. As such, each compound listed has different biological activities that each member of the class cannot be substituted; one for the other, with the expectation that the same intended result would be achieved. Further, although the most of the compounds listed in claim 16 are similarly drawn to activating the retinoid pathway, the compounds do not meet the criteria of (B)(1), as they do not share, one with another, a common core

structure. Accordingly, unity of invention between the compounds of the instant application is lacking and each compound claimed is considered to constitute a special technical feature.

With regard to Applicant disagreeing with the restriction of a combination of growth factors of claim 18 and that the restriction should be a species election (Applicant's response, page 10), Applicant's arguments are not persuasive. The combination of growth factors used in claim 18 do not share a special technical feature as each of the combinations of growth factors used in claim 18 have different biological effects.

With regard to Applicant disagreeing that the claims of Group 1 comprise many distinct methods, and that the restriction should be a species election (Applicant's response, page 10), Applicant's arguments are not persuasive. Each of the methods had been restricted accordingly because there was no special technical feature between the various methods.

The requirement is still deemed proper and is therefore made FINAL.

With regard to the additional restriction requirements, Applicant elects:

Nurr1 as the nuclear receptor (claim 2);

DNA encoding the Nurr1 nuclear receptor (claim 4);

an activator of retinoid X receptor (claim 16)

bFGF, FGF8, and Shh as the combination of growth factors (claim 18);

methods to be carried out in vitro (claim 21);

early midbrain glial cells (claim 20);

treating a patient (claims 29 and 31);

and species elections:

Wnt-5a (claim 7)

antioxidant (claim 19).

As indicated above, the Examiner has withdrawn the restriction between RNA and DNA in claim 4.

Claims 3, 14, 22-24, 27, 46, 47, 52, 54, 56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on August 31, 2007.

Claims 1, 2, 4, 5, 7, 15, 16, 18-21, 26, 28, 29, 31, 32, 40 are under consideration.

The invention is drawn to an in vitro method of inducing dopaminergic neuronal development comprising expressing a transgene construct comprising a nucleic acid sequence encoding Nurr1 and treating the cell with Wnt-5a. The invention is also drawn to taking the neuronal cells from the claimed method and administering them to a patient.

Information Disclosure Statement

Applicant filed an Information Disclosure Statement (IDS) on October 13, 2006 and October 20, 2005. Both IDSes have been considered.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 5, 7, 15, 16, 18-21, 26, 28, 29, 31, 32, 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

an in vitro method of differentiating a rat E14.5 cell from the ventral mesencephala into a dopaminergic neuron, wherein the method comprises:

treating the cell with Wnt5a, wherein the cell differentiates into a TH expressing cell,

does not reasonably provide enablement for

an in vitro method of differentiating any stem, neural stem, progenitor, precursor, or neural cell from any species of animal, other than rat, wherein the method comprises:

introducing a transgene construct comprising a nucleic acid sequence encoding Nurr-1 into the cell,

and treating the cell with any Wnt ligand,

wherein the cell differentiates into a dopaminergic neuron.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claims broadly encompass the use of any stem, neural stem, progenitor, precursor, or neural cell from any species of animal. At the time of filing, the art teaches that differentiation of an undifferentiated cell into a specific cell type was unpredictable. For example, Rothstein and Snyder, 2004, Nature Biotechnology, 22: 283-285 teach

while progress is being made in instructing the differentiation of ES cells toward particular cell types, knowledge of the relevant developmental mechanisms remains incomplete (Rothstein and Snyder, page 283, 3rd col., 1st parag. under "From whence the cells?"). To further illustrate this issue, Chung et al., 2002, European Journal of Neuroscience, 16: 1829-1838 teach two studies wherein different types of undifferentiated cells require different factors to induce tyrosine hydroxylase (TH) expression. Sakurada et al., 1999, Development, 126: 4017-4026 demonstrated that Nurr1 binds directly to the TH gene promoter in adult hippocampal precursors, resulting in induction of TH, in the absence of neuronal differentiation and without the expression of other DA markers. Wagner et al., 1999, Nature Biotechnology, 17: 653-659, see IDS, showed that Nurr1 can induce TH expression in C17.2 (cerebellum-derived immortalized) cells only when cocultured with ventral mesencephalic type 1 astrocytes. Chung et al. point out that both studies used partially committed precursors; however, the observed difference may be due to the specific characteristics of those cells (Chung et al., page 1829, 2nd col., 2nd parag. to page 1830). As these issues apply to the instant invention, while the specification teaches differentiation of rat E14.5 cells from the ventral mesencephala, the specification does not provide guidance to practice the claimed invention for other undifferentiated, or less differentiated cell types such as stem cells or progenitor cells, particularly since Sakurada et al. and Wagner et al. teach that different cell types require different factors for differentiation into TH expressing neurons. In addition to this, neither the specification nor the art provide guidance that introducing a Nurr1 expression construct and Wnt-5a are sufficient to induce a stem cell

to develop into dopaminergic neuron. Again, referring to the teachings of Sakurada et al. and Wagner et al., there are different requirements to induce a cell to develop into a dopamineric neuron. Wagner et al. teach that supernatant from ventral mesencephalic type 1 neurons could induce dopamine neuron formation in C17.2 cells. While the specification teaches that the supernatant contains Wnt-5a (specification, page 59, line 11), the teaching does not indicate that only Wnt-5a is required for TH expression in C17.2 cells, such that claim 1 could be practiced. As such, it cannot be determined whether only Wnt-5a is required to practice claim 1 in C17.2 cells or if other factors in the supernatant are required for TH expression. In addition to these issues, the claims are drawn to other factors which could be used to differentiate cells into dopaminergic cells, such as an activator of RXR (claim 16), bFGF/FGF8/Shh (claim 18), antioxidants (claim 19) or early glial cells (claim 20). Given the teachings of Sakaruda et al. and Wagner et al., wherein different cells require different conditions for induction, an artisan cannot readily extrapolate which cell types should be treated with other factors such as an activator of RXR or antioxidants without further guidance. Finally, while Sakurada et al. and Wagner et al.'s teachings indicate that TH expressing cells were produced in their experiments, neither of the teachings indicates that the TH expressing cells can be transplanted into a host and survive. (See below for discussion regarding the enablement of transplants of dopaminergic cells.) Sakurada et al., the cells express TH, but do not differentiate into neurons or express any other dopaminergic (DA) markers. In Wagner et al. and the instant specification, the teachings indicate that TH was induced in the Wnt-5a treated, rat E14.5 ventral mesencephala cells; however, there is

no guidance that the treated cells differentiate into dopaminergic neurons that survive transplantation (i.e., differentiate and integrate into the brain). The specification, pages 63-64, teach that the same genes were studied in Sakurada et al., Figure 1. Given that Sakurada et al. teach that their treated cells did not differentiate into neurons or express any other dopaminergic neurons and that the specification teaches the same genes were detected as Sakurada et al. are indicative that the specification does not provide guidance that the cells in the specification were dopaminergic cells that could be transplanted into a host. Transplantation is an issue since the invention is drawn to using the cells obtained from the claimed method and administering them to a patient (see claim 31).

In addition to this issue, the claims are also readable on transdifferentiating a neuronal cell to become a dopaminergic cell. At the time of filing, Liu and Rao, 2003, Journal of Cellular Biochemistry, 88: 29-40, transdifferentiation is not routine in the art. Rather, transdifferentiation of cells is not reliable or reproducible and requires complex manipulations (Liu and Rao, abstract). As this applies to the instant invention, while the claims envision that any neuronal cell could be used in the claimed invention, the art teaches that transdifferentiation of a variety of neuron to a cell type of interest is not routine in the art. Because the specification does not provide guidance on how to transdifferentiate any neuron to a dopaminergic cell, the specification is not enabled for this aspect of the invention.

The claims broadly encompass the use of cells from any species of animal. However, at the time of filing, the art teaches that cells from different species of animals

behave differently and respond to external cues differently. Ostenfeld et al., 2002, Developmental Brain Research, 134: 43-55 teach that rodent neurospheres isolated from the cortex and the striatum grew faster than those from the mesencephalon, but stopped growing after only 8 to 10 doublings. In contrast, human neurospheres under identical culture conditions continued to grow for over 40 population doublings. While rat neurospheres generated high numbers of oligodendrocytes, very few were found to develop from human neurospheres from any region after a few weeks of passage. Ostenfeld et al. teach that the data show that rat and human neurospheres have unique characteristics with regard to growth and differentiation. In another example, the art teaches that while mouse embryonic stem (ES) and embryonic germ (EG) cells can be grown in LIF, human EC cells, rhesus monkey ES cells, and human ES cells will not respond to LIF (Pera et al., 2000, Journal of Cell Science, 113: 5-10, page 8, 2nd col., 2nd parag.). As these issues apply to the instant invention, the claims broadly encompass using cells from any species of animal; however post-filing art teaches that similar populations of cells from different species of animals behave differently in the same culture conditions and as such, an artisan cannot reasonably predict that one culture condition can be used to obtain differentiated cells in different species of animals. Nothing in the specification provides guidance for an artisan to obtain cells from any species of animal and differentiate them into specific cell types under specific culture conditions. As such, the specification does not provide sufficient guidance for an artisan to arrive at the claimed invention without undue experimentation.

The claims encompass the use of any Wnt protein to differentiate a neural stem,

progenitor or precursor, or other stem or neural cell, in the presence of Nurr1, into a dopaminergic neuron. At the time of filing, since nothing in the art teaches that any Wnt protein was used with Nurr1 to arrive at dopaminergic cells, an artisan would turn to the specification for guidance of Wnt proteins that differentiate a cell into a dopamineric cell. According to the specification, Wnt-5a was the only Wnt that differentiated cells from rat E14.5 ventral mesencephala, while other Wnts had other biological functions. As such, the specification teaches that not all Wnts have the same function and thus, the claims are limited to treatment of cells from rat E14.5 ventral mesencephala with Wnt-5a.

With regard to the claims being drawn to a method of treating an individual comprising administering the composition of dopaminergic cells made by the claimed method (e.g. claim 31), nothing in the art or the specification provide any guidance to enable this aspect of the claimed invention. At the time of filing, Lindvall, 2001, The Lancet Supplement, 358: S47 teaches that transplanted dopaminergic neurons generated from embryonic stem cells and from stem cells in fetal brain survive only for a short time after grafting in animals. Lindvall also teach that success of transplantation is unclear as it is unclear whether the transplanted cells function as normal dopamine neurons and that little is known about human cells because most studies have used rodent stem cells. In another publication, Arenas, 2005, Annals of the New York Academy of Sciences, 1049, pages 51-66; printout, 27 pages, teaches that cell replacement therapies for Parkinson's disease are not routine in the art. Problems include inflammatory or immune reaction, selecting the site of transplantation, the number of cells per site, and cell migration. These factors may lead to a patchy

distribution of cells that result in an irregular innervation of target structures and an uneven dopaminergic (DA) neurotransmission that could favor the appearance of dyskinesias (Arenas, page 5 of printout). Because the art teaches that treatment using dopaminergic neurons are not routine in the art, an artisan is not enabled for this aspect of the invention.

With regard to claim 40 being drawn to treatment of any neuronal loss or any neurodegenerative disease, the specification and art teach a relationship between dopaminergic neurons and Parkinson's disease. However, nothing in the specification or art teach a relationship between dopaminergic neurons and other neurodegenerative diseases (e.g. Alzheimer's disease) such that the cells obtained from the method of claim 1 could be used to treat those other neurodegenerative diseases.

As such, the claims are rejected.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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